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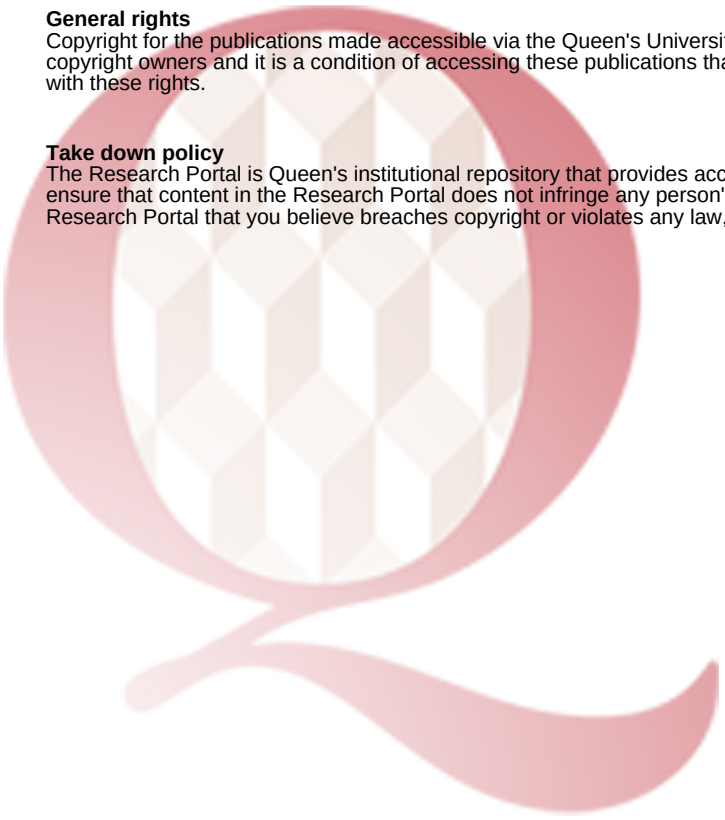

Digoxin use after diagnosis of colorectal cancer and survival: A population-based cohort study

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Abstract

Background: Digoxin has been shown to be impact on a number of pathways that are of relevance to cancer and its use has been associated with increased risks of breast and uterus cancer and, more recently, a 40% increase in colorectal cancer risk. These findings raise questions about the safety of digoxin use in colorectal cancer patients and therefore we investigated whether digoxin use after colorectal cancer diagnosis increased the risk of colorectal cancer-specific mortality.

Methods: A cohort of 10,357 colorectal cancer patients newly diagnosed from 1998 to 2009 was identified from English cancer registries and linked to the UK Clinical Practice Research Datalink (to provide digoxin and other prescription records) and to the Office of National Statistics mortality data (to identify 2,724 colorectal cancer-specific deaths). Using time-dependent Cox regression models, unadjusted and adjusted hazard ratios (HR) and 95% confidence intervals (CIs) were calculated for the association between post-diagnostic exposure to digoxin and colorectal cancer-specific mortality.

Results: Overall, 682 (6%) colorectal cancer patients used digoxin after diagnosis. Digoxin use was associated with a small increase in colorectal cancer-specific mortality before adjustment (HR=1.25; 95% CI 1.07-1.46), but after adjustment for confounders the association was attenuated (adjusted HR=1.10; 95% CI 0.91-1.34) and there was no evidence of a dose response.

Conclusions: In this large population-based colorectal cancer cohort, there was little evidence of an increase in colorectal cancer-specific mortality with digoxin use after diagnosis.

Impact: These results provide some reassurance that digoxin use is safe in colorectal cancer patients.

Introduction

The main effect of digoxin, a cardiac glycoside, is on the inhibition of the sodium potassium ATPase pump but it impacts a number of pathways relevant to cancer. For instance, studies have shown increases in breast and uterus cancer probably related to estrogenic effects of digoxin (1). A recent large UK study reported a 40% increase in colorectal cancer risk in digoxin users (2), which the researchers suggest possibly reflect direct effects of the sodium potassium ATPase pump on tumorigenic pathways such as the Src/mitogen-activated proteinkinase (M APK) (3). In addition, preclinical studies have found that digoxin may reduce chemotherapy efficacy (4). These findings raise questions about the safety of digoxin in colorectal cancer patients. As there has been little research into digoxin use and colorectal cancer progression, we investigated whether colorectal cancer patients using digoxin had increased colorectal cancer-specific mortality.

Materials and Methods

The data source and methods have been discussed in detail previously (5). In brief, patients with newly diagnosed colorectal cancer from English cancer registries between 1998 and 2009 were identified from the National Cancer Data Repository (NCDR). Colorectal cancer-specific deaths up to January 2012 were identified from the underlying cause of death from Office of National Statistics (ONS) death registration data. The Clinical Practice Research Datalink (CPRD) provided digoxin use from GP prescribing records. Potential confounders including stage, grade and treatment were determined from NCDR. Smoking, BMI, deprivation and comorbidities were determined from GP records.

Statistical analysis

Patients were followed up from one year after colorectal cancer diagnosis until death, end of GP registration, last date of data collection from GP, or end of ONS follow-up. In the main analysis, time-dependent Cox regression models were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for colorectal cancer-specific death for digoxin users compared with non-users using a time varying covariate (lagged by 6 months). Adjusted analyses were conducted including potential confounders. Further analyses were conducted by number of digoxin prescriptions and number of DDDs. Analyses were repeated for all-cause mortality. Analyses were conducted in STATA 13.

Results

The final cohort included 10,357 colorectal cancer patients with mean of 4.8 years of follow-up from diagnosis (maximum=14 years) containing 2,724 colorectal cancer-specific deaths, and 1,263 deaths from other causes. Table 1 shows characteristics by digoxin use. Digoxin use was associated with increased colorectal cancer-specific mortality before adjustment (HR=1.25; 95% CI 1.07-1.46) but after adjustment for confounders the association was attenuated (adjusted HR=1.10; 95% CI 0.91-1.34) and no dose response associations were apparent. After adjustment for confounders there was an increase in all-cause mortality in digoxin users (HR=1.53; 95% CI 1.34-1.73). This increase was most marked for cardiovascular deaths (adjusted HR=2.73; 95% CI 2.11-3.52), as expected, and there was only a small increase in the risk of death for non-cardiovascular causes (adjusted HR=1.26; 95% CI 1.08-1.47) (Table 2). A simplified analysis for colorectal cancer-specific mortality, based upon digoxin use in the year after diagnosis, also revealed little evidence of association (adjusted HR=0.98; 95% CI 0.79- 1.22). A further sensitivity analyses revealed little

evidence of association between colorectal cancer-mortality and digoxin use in the year before diagnosis (adjusted HR=0.88; 95% CI 0.73- 1.06).

Discussion

We observed little evidence of increased colorectal cancer-specific mortality in digoxin users providing some reassurance that digoxin is safe in colorectal cancer patients, despite recent evidence that digoxin users may have increased colorectal cancer risk (2). Our findings do not support a French study which observed reduced overall mortality with digoxin in 75 colorectal cancer patients (6), nor some pre-clinical studies suggesting that digoxin could have inhibitory effects on colorectal cancer cell growth (7).

This study is the first population-based cohort to investigate digoxin use and colorectal cancer-specific mortality. Other strengths include large size and long duration of follow-up but we cannot rule out the possibility of type 2 error (a power calculation, using Schoenfeld's method, based on observed medication use and cancer-specific deaths, indicated that we had approximately 80% power to detect as significant a HR of 1.25 for digoxin). Although verification of cancer diagnosis and death were robust, misclassification of colorectal cancer cause of death is possible; however, methodological studies suggest that comparative risk estimates are unlikely to be greatly affected where misclassification is unlikely to be differential. Recall bias was eliminated by using routinely collected GP-prescribed drug. Confounding by indication, often a problem in pharmacoepidemiology, is unlikely to have influenced our main finding for colorectal cancer-specific mortality, but would explain the increase in all-cause mortality due largely to raised cardiovascular mortality in digoxin users (8). Misclassification of digoxin usage is possible because of non-compliance. As with all observational studies, confounding caused by unrecorded or incomplete potential

confounders (e.g. stage) cannot be ruled out. In conclusion, there was little evidence of an increase in colorectal cancer-specific mortality with digoxin use after diagnosis.

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References

1. Biggar RJ. Molecular pathways: digoxin use and estrogen-sensitive cancers--risks and possible therapeutic implications. Clin Cancer Res. 2012;18:2133–7.
2. Ben Boursi, Kevin Haynes, Ronac Mamtani, Yu-Xiao Yang. Digoxin use and the risk for colorectal cancer. Pharmacoepidemiol Drug Saf. 2014;23:1147–53.
3. Li Z, Zhang Z, Xie JX, Li X, Tian J, Cai T, et al. Na/K-ATPase mimetic pNaKtide peptide inhibits the growth of human cancer cells. J Biol Chem. 2011;286:32394–403.
4. Riganti C, Campia I, Polimeni M, Pescarmona G, Ghigo D, Bosia A. Digoxin and ouabain induce P-glycoprotein by activating calmodulin kinase II and hypoxia-inducible factor-1alpha in human colon cancer cells. Toxicol Appl Pharmacol. 2009;240:385-92.
5. Cardwell CR, Hicks BM, Hughes C, Murray LJ. Statin use after colorectal cancer diagnosis and survival: a population-based cohort study. J Clin Oncol. 2014;32:1–11.
6. Menger L, Vacchelli E, Adjemian S, Martins I, Ma Y, Shen S, et al. Cardiac glycosides exert anticancer effects by inducing immunogenic cell death. Sci Transl Med. 2012;4:143ra99.
7. Felth J, Rickardson L, Rosén J, Wickström M, Fryknäs M, Lindskog M, et al. Cytotoxic effects of cardiac glycosides in colon cancer cells, alone and in combination with standard chemotherapeutic drugs. J Nat Prod. 2009;72:1969–74.
8. Vidaillet H, Granada JF, Chyou P, Maassen K, Ortiz M, Pulido JN, et al. A population-based study of mortality among patients with atrial fibrillation or flutter. Am J Med. 2002;113:365–70.

Table 1. Characteristics of colorectal cancer patients by digoxin use after diagnosis.

Characteristics	Digoxin use after diagnosis		Digoxin use in first year after diagnosis	
	Ever n (%)	Never n (%)	Ever n (%)	Never n (%)
Year of diagnosis: 1998-2000	149 (22)	1,599 (17)	94(19)	1,654(17)
2001-2003	233 (34)	2,345 (24)	149(30)	2,429(25)
2004-2006	173 (25)	2,724 (28)	140(28)	2,757(28)
2007-2009	127 (19)	3,007 (31)	112(23)	3,022(31)
Age at diagnosis: < 50	3 (0)	610 (6)	1(0)	612(6)
50-59	20 (3)	1,463 (15)	10(2)	1,473(15)
60-69	90 (13)	2,683 (28)	50(10)	2,723(28)
70-79	299 (44)	3,204 (33)	216(44)	3,287(33)
80-89	245 (36)	1,585 (16)	198(40)	1,632(17)
≥ 90	25 (4)	130 (1)	20(4)	135(1)
Gender: Males	379 (56)	5,353 (55)	272 (55)	5,460 (55)
Stage: I	93 (18)	1,229 (16)	61(16)	1,261(16)
II	240 (45)	3,004 (39)	173(45)	3,071(39)
III	177 (33)	2, 914 (38)	134(35)	2,957(38)
IV	19 (4)	524 (7)	15 (4)	528 (7)
Missing	153	2,004	112	2,045
Grade: Well	33 (6)	547 (7)	22(6)	585(6)
Moderately	445 (78)	6,432 (78)	328(78)	6,549(79)
Poorly	92 (16)	1,259 (15)	62(16)	1,279(15)
Missing	*112*	*1,420*	*83*	*1,449*
Treatment within 6 months of cancer diagnosis				
Surgery	588 (86)	8,510 (88)	425(86)	8,673(88)
Chemotherapy	88 (13)	3,054 (32)	63(13)	3,079(31)
Radiotherapy	64 (9)	1,381 (14)	48(10)	1,397(14)
Smoking status prior to cancer diagnosis				
Non-smoker	232 (52)	3,498 (53)	169(51)	3,561(53)
Ex-smoker	167 (37)	2,145 (32)	128(39)	2,184(32)
Current smoker	48 (11)	969 (15)	33(10)	984(15)
Missing	*235*	*3,063*	*165*	*3,133*
Alcohol consumption prior to diagnosis				
Never	87 (20)	1,007 (16)	66(21)	1,028(16)
Ever	351 (80)	5,443 (84)	255(79)	5,539(84)
Missing	*244*	*3,225*	*174*	*3,295*
BMI (kg/m^2) prior to diagnosis: mean (sd)	27.0 (4.8)	26.5 (4.7)	26.9(5.1)	26.5(4.7)
Underweight (<18.5)	6 (1)	126 (2)	5(2)	127(2)
Normal (18.5 to 25)	147 (34)	2,407 (37)	114(36)	2,440(37)
Overweight (25-30)	185 (43)	2,654 (41)	130(41)	2,709(41)
Obese (>30)	93 (22)	1,258 (20)	68(21)	1,283(20)
Missing	*251*	*3,230*	*178*	*3,303*
Deprivation fifth: 1st (least deprived)	149 (22)	2,498 (26)	112(23)	2,535(26)
2nd	173 (25)	2,389 (25)	125(25)	2,437(25)
3rd	151 (22)	1,986 (21)	105(21)	2,032(21)
4th	121 (18)	1,694 (18)	85(17)	1,730(18)
5th (most deprived)	86 (13)	1,091 (11)	66(13)	1,111(11)
Missing	*2*	*17*	*2*	*17*
Comorbidity prior to cancer diagnosis				
Cerebrovascular disease	61 (9)	390 (4)	49(10)	402(4)
Chronic pulmonary disease	106 (16)	1,182 (12)	69(14)	1,219(12)
Congestive heart disease	85 (12)	183 (2)	72(15)	196(2)
Diabetes	102 (15)	758 (8)	83(17)	777(8)
Myocardial infarction	47 (7)	369 (4)	39(8)	377(4)
Peptic ulcer disease	39 (6)	398 (4)	27(5)	410(4)
Peripheral vascular disease	34 (5)	256 (3)	28(6)	262(3)
Renal disease	31 (5)	353 (4)	25(5)	359(4)
Medication after diagnosis [a]				
Low dose aspirin use (after diagnosis, in exposure period)	283 (42)	2,349 (24)	188 (38)	2,444 (25)
Statins use	206 (30)	2,570 (27)	148 (30)	2,628 (27)
Metformin use	75 (11)	637 (7)	53 (11)	659 (7)
ACEI use	279 (41)	2,241 (23)	186 (38)	2,334 (24)

ACEI=angiotensin-converting-enzyme inhibitor

[a] Medication use calculated in the first year after diagnosis for the comparison of digoxin users and non-users in the first year after diagnosis.

Table 2. Association between digoxin usage after cancer diagnosis and colorectal cancer -specific and all-cause mortality.

Medication usage after diagnosis	Cancer-specific/ all-cause mortality	All patients	Person years	Unadjusted HR (95%CI)	Adjusted[a] HR (95%CI)	Cohort with stage and deprivation		
						Unadjusted HR (95%CI)	Adjusted[a] HR (95%CI)	Fully adjusted[b] HR (95%CI)
Colorectal cancer-specific mortality								
Number of patients				[10,357]	[10,357]	[8,183]	[8,183]	[8,183]
Digoxin non-user	2,560	9,675	36,934	1.00	1.00	1.00	1.00	1.00
Digoxin user [c]	164	682	2,023	1.25 (1.07, 1.46)	1.18 (1.01, 1.40)	1.12 (0.92, 1.35)	1.11 (0.91, 1.36)	1.10 (0.91, 1.34)
Digoxin non-user	2,560	9,675	36,934	1.00	1.00	1.00	1.00	1.00
1 to 11 Digoxin prescriptions [d]	82	239	780	1.26 (1.01, 1.57)	1.19 (0.95, 1.49)	1.14 (0.88, 1.49)	1.15 (0.88, 1.50)	1.10 (0.84, 1.45)
≥ 12 Digoxin prescriptions [d]	82	443	1,243	1.24 (0.99, 1.55)	1.18 (0.94, 1.48)	1.09 (0.84, 1.43)	1.08 (0.82, 1.42)	1.10 (0.84, 1.44)
Digoxin non-user	2,560	9,675	36,934	1.00	1.00	1.00	1.00	1.00
1 to 365 ddds [d]	113	358	1,090	1.30 (1.07, 1.56)	1.22 (1.00, 1.47)	1.14 (0.90, 1.43)	1.14 (0.90, 1.45)	1.10 (0.87, 1.40)
≥ 365 ddds [d]	51	324	933	1.15 (0.87, 1.52)	1.12 (0.84, 1.49)	1.09 (0.79, 1.49)	1.06 (0.76, 1.47)	1.10 (0.79, 1.52)
All-cause mortality								
Number of patients				[10,357]	[10,357]	[8,183]	[8,183]	[8,183]
Digoxin non-user	3,613	9,675	36,934	1.00	1.00	1.00	1.00	1.00
Digoxin user [c]	374	682	2,023	1.96 (1.76, 2.18)	1.53 (1.37, 1.71)	1.92 (1.70, 2.17)	1.52 (1.34, 1.73)	1.52 (1.34, 1.73)
Digoxin non-user	3,613	9,675	36,934	1.00	1.00	1.00	1.00	1.00
1 to 11 Digoxin prescriptions [d]	157	239	618	1.81 (1.54, 2.13)	1.44 (1.22, 1.69)	1.78 (1.48, 2.15)	1.46 (1.20, 1.76)	1.43 (1.18, 1.72)
≥ 12 Digoxin prescriptions [d]	217	443	1,023	2.09 (1.82, 2.40)	1.60 (1.39, 1.85)	2.03 (1.73, 2.37)	1.58 (1.34, 1.86)	1.60 (1.36, 1.89)
Digoxin non-user	3,613	9,675	36,934	1.00	1.00	1.00	1.00	1.00
1 to 365 ddds [d]	224	358	864	1.91 (1.67, 2.19)	1.49 (1.29, 1.71)	1.86 (1.59, 2.18)	1.50 (1.27, 1.76)	1.47 (1.25, 1.73)
≥ 365 ddds [d]	150	324	777	2.04 (1.73, 2.41)	1.60 (1.35, 1.89)	2.00 (1.67, 2.41)	1.57 (1.30, 1.89)	1.61 (1.33, 1.95)

ddds, defined daily doses.

[a] Model includes year of diagnosis, age at diagnosis, gender, surgery within 6 months, radiotherapy within 6 months, chemotherapy within 6 months, site (colon or rectum), comorbidities prior to diagnosis (including cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, diabetes with complications, myocardial infarction, peptic ulcer disease, peripheral vascular disease, renal disease) and other medication use (after diagnosis, as time varying covariates, specifically low-dose aspirin, statins, metformin, and ACEIs).

[b] Model includes all variables in [a], additionally adjusted for stage and deprivation (in fifths) in individuals with non-missing values.

[c] Digoxin use modelled as a time varying covariate with an individual considered a non-user prior to 6 months after first digoxin usage and a user after this time, excludes deaths in the year after cancer diagnosis.

[d] Digoxin use modelled as a time varying covariate with an individual considered a non-user prior to 6 months after first medication usage, a user of 0 to 12 prescriptions (or 365th defined daily doses) from 6 months after first prescription to 6 months after 12th prescription (or 365th defined daily dose) and a greater user after this time, excludes deaths in the year after cancer diagnosis.